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THE SIGNIFICANCE OF POMEGRANATE PEEL AS AN ADJUNCT PHYTOTHERAPEUTIC AGENT IN THE MANAGEMENT OF LIVER DISEASES

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Abstract. Liver diseases, particularly metabolic dysfunction-associated steatotic liver disease, chronic liver injury following viral hepatitis, toxic hepatopathies, and fibrotic liver disorders, remain important challenges in modern medicine. In recent years, plant-derived products rich in natural polyphenols have attracted scientific attention because of their potential to reduce oxidative stress, inflammation, and lipid metabolic disturbances in hepatocytes. Pomegranate peel contains biologically active compounds such as punicalagin, ellagic acid, gallic acid, flavonoids, and tannins, which have demonstrated antioxidant, anti-inflammatory, antifibrotic, and metabolic regulatory properties in experimental studies and a limited number of clinical trials. The purpose of this article is to analyze the possible significance of pomegranate peel in the management of liver diseases on the basis of current scientific literature, to describe its biochemical mechanisms, and to evaluate the limitations of its clinical use. The literature suggests that pomegranate peel extract should not be considered an independent treatment for liver diseases. Rather, it may be studied as an adjunct to standard dietary modification, physical activity, control of metabolic risk factors, and etiological treatment.

Keywords: Pomegranate peel, Punica granatum, liver diseases, metabolic dysfunction-associated steatotic liver disease, oxidative stress, punicalagin, ellagic acid, phytotherapy.

ЗНАЧЕНИЕ КОЖУРЫ ГРАНАТА КАК ВСПОМОГАТЕЛЬНОГО ФИТОТЕРАПЕВТИЧЕСКОГО СРЕДСТВА ПРИ ЗАБОЛЕВАНИЯХ ПЕЧЕНИ

Аннотация. Заболевания печени, особенно метаболически ассоциированная жировая болезнь печени, хронические поражения печени после вирусных гепатитов, токсические гепатопатии и фиброзные процессы, остаются актуальной проблемой современной медицины. В последние годы растительные продукты, богатые природными полифенолами, активно изучаются с точки зрения их способности уменьшать оксидативный стресс, воспаление и нарушения липидного обмена в гепатоцитах. Кожура граната содержит такие биологически активные соединения, как пуникалагин, эллаговая кислота, галловая кислота, флавоноиды и танины, которые в экспериментальных и отдельных клинических исследованиях проявляли антиоксидантные, противовоспалительные, антифибротические и метаболически регулирующие свойства. Цель данной статьи заключается в анализе возможного значения кожуры граната при заболеваниях печени на основе научной литературы, раскрытии ее биохимических механизмов и оценке границ клинического применения. Анализ литературы показывает, что экстракт кожуры граната не следует рассматривать как самостоятельный метод лечения заболеваний печени. Более обоснованным является его изучение в качестве вспомогательного средства на фоне

стандартной диетотерапии, физической активности, контроля метаболических факторов риска и этиологического лечения.

Ключевые слова: Кожура граната, Punica granatum, заболевания печени, метаболически ассоциированная жировая болезнь печени, оксидативный стресс, пуникалагин, эллаговая кислота, фитотерапия.

ANOR PO‘STINING JIGAR KASALLIKLARINI DAVOLASHDA QO‘SHIMCHA FITOTERAPEVTIK VOSITA SIFATIDAGI AHAMIYATI

Annotatsiya. Jigar kasalliklari, ayniqsa metabolik disfunksiya bilan bog‘liq yog‘li jigar kasalligi, virusli gepatitlardan keyingi surunkali jigar shikastlanishlari, toksik gepatopatiyalar va fibroz jarayonlari zamonaviy tibbiyotning dolzarb muammolaridan biri bo‘lib qolmoqda. So‘nggi yillarda tabiiy polifenollarga boy o‘simlik mahsulotlari jigar hujayralarida oksidlovchi stress, yallig‘lanish va lipid almashinuvi buzilishlarini kamaytirish imkoniyati nuqtai nazaridan o‘rganilmoqda. Anor po‘sti tarkibida punikalagin, ellag kislotasi, gall kislotasi, flavonoidlar va taninlar kabi biologik faol birikmalar mavjud bo‘lib, ular antioksidant, yallig‘lanishga qarshi, antifibrotik va metabolik regulyator ta’sirlarga ega ekanligi eksperimental va ayrim klinik tadqiqotlarda ko‘rsatilgan. Ushbu maqolaning maqsadi anor po‘stining jigar kasalliklarini davolashdagi ehtimoliy ahamiyatini ilmiy adabiyotlar asosida tahlil qilish, uning biokimyoviy mexanizmlarini yoritish va klinik amaliyotda qo‘llash chegaralarini baholashdan iborat. Adabiyotlar tahlili shuni ko‘rsatadiki, anor po‘sti ekstrakti mustaqil davo vositasi sifatida emas, balki standart parhez, jismoniy faollik, metabolik xavf omillarini nazorat qilish va etiologik davolashga qo‘shimcha vosita sifatida o‘rganilishi maqsadga muvofiqdir.

Kalit so‘zlar: Anor po‘sti, Punica granatum, jigar kasalliklari, metabolik yog‘li jigar kasalligi, oksidlovchi stress, punikalagin, ellag kislotasi, fitoterapiya.

Introduction

Liver diseases represent a broad group of pathological conditions in which hepatocytes, biliary structures, hepatic stellate cells, immune cells, and vascular components of the liver are affected by metabolic, viral, toxic, autoimmune, or cholestatic mechanisms. In clinical practice, chronic liver injury often develops gradually and may remain asymptomatic until biochemical abnormalities, hepatic steatosis, fibrosis, portal hypertension, or cirrhosis become evident. Among these conditions, metabolic dysfunction-associated steatotic liver disease, formerly widely known as non-alcoholic fatty liver disease, has gained particular importance because of its strong association with obesity, insulin resistance, dyslipidemia, arterial hypertension, and type 2 diabetes mellitus [1].

The modern management of liver diseases is primarily based on etiological diagnosis and evidence-based treatment. Viral hepatitis requires antiviral therapy when indicated, autoimmune liver diseases require immunosuppressive strategies, cholestatic disorders need disease-specific management, and metabolic liver disease requires long-term lifestyle correction and control of cardiometabolic risk factors [1, 2]. At the same time, interest in adjunctive natural compounds has increased because oxidative stress, chronic low-grade inflammation, mitochondrial dysfunction, intestinal dysbiosis, and fibrogenic signaling are shared mechanisms in many liver diseases. This scientific interest does not mean that herbal products can replace standard therapy. Instead, it reflects the need to identify safe and biologically plausible supportive agents that may improve metabolic and inflammatory parameters when used responsibly.

Pomegranate, known botanically as Punica granatum L., has been used in traditional nutrition and folk medicine for centuries. The peel, which is often treated as a by-product of fruit processing, is particularly rich in polyphenolic compounds. Compared with the edible arils and juice, the peel contains concentrated amounts of hydrolyzable tannins, especially punicalagin and punicalin, as well as ellagic acid, gallic acid, catechins, flavonoids, and other phenolic compounds [3, 4]. These substances are of interest in hepatology because they may influence oxidative stress, lipid peroxidation, inflammatory cytokine production, hepatic lipid accumulation, and collagen deposition.

Experimental studies have shown that pomegranate peel extract can reduce biochemical and histological signs of liver injury in models of carbon tetrachloride-induced hepatotoxicity, acetaminophen-induced liver injury, high-fat diet-induced fatty liver, and hepatic fibrosis [5, 6]. More recently, human clinical trials have evaluated pomegranate peel supplementation in patients with fatty liver disease and metabolic risk factors. These trials suggest possible improvements in body weight, waist circumference, lipid profile, fasting blood glucose, inflammatory markers, liver enzymes, and steatosis grade, although the available evidence remains limited in duration, sample size, and generalizability [7, 8].

The relevance of this topic is especially important for regions where pomegranate is widely available and used in daily nutrition. However, the clinical use of pomegranate peel must be discussed carefully. The liver is the central organ of xenobiotic metabolism, and not every natural product is automatically safe for patients with chronic liver disease. International hepatology guidelines emphasize that herbal and dietary supplements may themselves be associated with liver injury in some circumstances [9]. Therefore, any discussion of pomegranate peel in liver disease should combine pharmacological interest with clinical caution.

The purpose of this article is to analyze the significance of pomegranate peel in the management of liver diseases using available scientific literature, to describe its possible hepatoprotective mechanisms, and to define the practical limitations of its use as an adjunct phytotherapeutic agent.

Materials and Methods

This article was prepared as a narrative literature review based on scientific publications addressing pomegranate peel, Punica granatum L., polyphenols, oxidative stress, inflammation, liver injury, fatty liver disease, and hepatic fibrosis. The analysis included experimental studies, clinical trials, systematic reviews, and hepatology guidelines relevant to the potential use of pomegranate peel in liver diseases.

The literature was evaluated according to thematic relevance and scientific strength. Greater attention was given to studies that directly investigated pomegranate peel extract or pomegranate-derived polyphenols in liver-related outcomes. Experimental studies were used to describe possible biological mechanisms, whereas clinical trials were used to discuss practical implications for human liver disease. Guidelines and hepatology reviews were included to ensure that the interpretation remained clinically balanced and did not overstate the therapeutic role of phytotherapy.

The reviewed evidence was grouped into several conceptual areas. The first area included phytochemical composition of pomegranate peel. The second area focused on mechanisms of hepatoprotection, including antioxidant activity, anti-inflammatory effects, lipid metabolism regulation, modulation of hepatic stellate cell activation, and antifibrotic pathways. The third area analyzed experimental liver injury models. The fourth area examined available clinical evidence,

especially in metabolic fatty liver disease. The fifth area considered safety, limitations, and prospects for future research.

Literature Review

Pomegranate peel has attracted scientific attention because it is one of the richest parts of the fruit in polyphenolic compounds. The peel contains punicalagin, punicalin, ellagic acid, gallic acid, catechins, anthocyanins, flavonoids, and condensed tannins. Punicalagin is considered one of the characteristic ellagitannins of pomegranate peel and may be hydrolyzed into ellagic acid, which can undergo further metabolism by the intestinal microbiota into urolithins [3, 4]. This metabolism is important because the biological effect of pomegranate polyphenols depends not only on their chemical composition but also on intestinal absorption, microbial transformation, hepatic metabolism, and systemic bioavailability.

The antioxidant potential of pomegranate peel is one of the most frequently described mechanisms in experimental literature. Oxidative stress plays a central role in hepatocyte injury because excessive reactive oxygen species can damage cellular membranes, mitochondrial proteins, DNA, and lipids. In fatty liver disease, oxidative stress contributes to the transition from simple steatosis to steatohepatitis. In toxic liver injury, it amplifies necrosis and inflammation. In fibrotic liver disease, it stimulates hepatic stellate cells and promotes extracellular matrix deposition. Pomegranate peel polyphenols may reduce lipid peroxidation, support endogenous antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, and decrease malondialdehyde levels in experimental models [5, 6].

Inflammation is another key target. Chronic liver diseases are often accompanied by activation of Kupffer cells, recruitment of inflammatory cells, and increased expression of cytokines such as tumor necrosis factor alpha, interleukin 6, and transforming growth factor beta. Punicalagin and ellagic acid have been described as compounds capable of influencing inflammatory signaling pathways, including nuclear factor kappa B and mitogen-activated protein kinase pathways [4, 10]. By reducing inflammatory signaling, pomegranate peel extract may theoretically limit hepatocyte damage and slow the progression of fibrogenesis.

The relationship between pomegranate peel and lipid metabolism is particularly relevant to metabolic fatty liver disease. Hepatic steatosis develops when lipid influx and de novo lipogenesis exceed fatty acid oxidation and lipid export. Experimental studies suggest that pomegranate peel polyphenols may influence lipid accumulation in hepatocytes and improve lipid-related parameters [11]. Human trials in fatty liver disease have also reported improvement in triglycerides, total cholesterol, low-density lipoprotein cholesterol, body weight, waist circumference, and liver steatosis markers when pomegranate peel extract was combined with calorie restriction [7, 8]. These findings support the view that pomegranate peel is more likely to be beneficial in metabolic liver disease than as a direct etiological treatment for viral, autoimmune, or advanced cirrhotic conditions.

Experimental antifibrotic effects are another important part of the literature. In carbon tetrachloride-induced liver fibrosis models, pomegranate peel extract has been associated with lower levels of hydroxyproline, hyaluronic acid, laminin, procollagen type III, and transforming growth factor beta 1, as well as improved histological appearance of liver tissue [5]. These results indicate that pomegranate peel may influence pathways involved in collagen deposition and hepatic stellate cell activation. However, such findings should be interpreted with caution because animal models do not fully reproduce the complexity of human chronic liver disease.

Clinical evidence remains limited but promising. A randomized double-blind clinical trial conducted among patients with non-alcoholic fatty liver disease reported that 1500 mg of

pomegranate peel extract daily for eight weeks, together with a calorie-deficit diet, improved metabolic syndrome risk factors and reduced hepatic steatosis [7]. Another double-blind placebo-controlled randomized clinical trial published in Phytotherapy Research reported favorable effects of pomegranate peel consumption on liver enzymes, lipid profile, liver steatosis, and high-sensitivity C-reactive protein in patients with fatty liver disease [8]. A recent meta-analysis of pomegranate intake also suggested that longer interventions may reduce aspartate aminotransferase and alanine aminotransferase, especially in obese individuals or patients with metabolic disorders [12]. Nevertheless, these findings do not establish pomegranate peel as a standard treatment. They indicate that further larger, longer, and better-standardized clinical trials are needed.

Safety must be considered separately. Herbal and dietary supplements are often perceived as harmless because they are natural. This perception is scientifically incorrect. The liver metabolizes many plant-derived compounds, and some herbal products have been associated with hepatotoxicity, drug interactions, contamination, or unpredictable effects in vulnerable patients [9]. Pomegranate peel is rich in tannins, and excessive or poorly standardized use may cause gastrointestinal discomfort, constipation, nausea, or potential interaction with medications. Patients with chronic liver disease, cirrhosis, cholestasis, pregnancy, lactation, anticoagulant therapy, polypharmacy, or renal impairment should not use concentrated extracts without medical supervision.

Results

The analysis of available literature shows that pomegranate peel has several biologically plausible mechanisms that may support liver health. These mechanisms are mainly connected with its high polyphenol content and include reduction of oxidative stress, inhibition of lipid peroxidation, attenuation of inflammatory signaling, improvement of lipid metabolism, and possible modulation of fibrogenic pathways.

The strongest mechanistic evidence comes from experimental studies. In toxic and fibrotic liver injury models, pomegranate peel extract reduced aminotransferase activity, improved histological signs of hepatic injury, decreased malondialdehyde levels, increased antioxidant enzyme activity, and reduced fibrosis-related markers [5, 6]. These findings are consistent with the biochemical nature of pomegranate peel, which contains potent antioxidant and anti-inflammatory compounds.

The most clinically relevant evidence relates to metabolic fatty liver disease. Human trials suggest that pomegranate peel extract, when used together with dietary intervention, may improve body composition, lipid profile, inflammatory markers, and steatosis indicators [7, 8]. This is important because metabolic fatty liver disease is closely linked to obesity, dyslipidemia, insulin resistance, and chronic inflammation. In this context, pomegranate peel may act not as a disease-specific drug but as a supportive metabolic modulator.

The evidence is less direct for viral hepatitis, alcoholic liver disease, autoimmune liver disease, cholestatic disease, and advanced cirrhosis. In these conditions, pomegranate peel cannot be considered an etiological or curative treatment. For example, chronic hepatitis B and C require antiviral strategies based on established clinical criteria. Autoimmune hepatitis requires immunosuppressive therapy. Primary biliary cholangitis and primary sclerosing cholangitis need disease-specific hepatological monitoring. Decompensated cirrhosis requires specialized care and sometimes liver transplantation evaluation. Pomegranate peel may be discussed only as a possible adjunct nutritional or antioxidant component after careful medical assessment.

The reviewed evidence also indicates several limitations. Many experimental studies use doses, extraction methods, and animal models that cannot be directly transferred to human patients. Clinical trials are still relatively few, short-term, and focused mainly on fatty liver disease.

Standardization of active compounds is inconsistent, and the concentration of punicalagin and ellagic acid may differ greatly depending on pomegranate variety, geographic origin, drying method, extraction solvent, storage conditions, and capsule production technology.

Discussion

The potential significance of pomegranate peel in liver diseases should be understood through the pathophysiology of chronic hepatic injury. Many liver diseases, despite different causes, share common downstream mechanisms. These mechanisms include oxidative stress, mitochondrial dysfunction, inflammatory activation, hepatocyte apoptosis or necrosis, stellate cell activation, and extracellular matrix deposition. Pomegranate peel polyphenols may influence several of these pathways at the same time, which explains why the plant product has attracted interest in hepatoprotective research.

Punicalagin is one of the most important compounds in pomegranate peel. It has a large molecular structure and strong antioxidant capacity. After ingestion, it may be transformed into ellagic acid and later into urolithins under the influence of gut microbiota. This process connects pomegranate peel not only with direct antioxidant mechanisms but also with the gut-liver axis. The gut-liver axis is especially important in metabolic liver disease because intestinal permeability, endotoxin exposure, dysbiosis, and inflammatory signaling may contribute to hepatic steatosis and steatohepatitis. Although this field requires more direct clinical evidence, it offers a biologically meaningful explanation for the systemic effects of pomegranate-derived polyphenols [3, 4].

The anti-inflammatory potential of pomegranate peel is also clinically relevant. In fatty liver disease, inflammation is a key factor that distinguishes simple steatosis from steatohepatitis. In toxic liver injury, inflammatory signaling amplifies hepatocyte damage. In chronic viral hepatitis, inflammation contributes to fibrosis progression even though antiviral therapy remains the cornerstone of treatment. Polyphenols may reduce inflammatory signaling by suppressing oxidative stress and influencing cytokine production. However, this does not mean that pomegranate peel can replace anti-inflammatory, antiviral, or immunomodulatory drugs when these are medically indicated.

The metabolic effects reported in clinical trials deserve particular attention. Improvement of body weight, waist circumference, lipid profile, fasting glucose, and inflammatory markers may indirectly benefit liver status in patients with fatty liver disease. In this sense, pomegranate peel extract may be viewed as a component of a broader metabolic correction strategy. Such a strategy should include calorie control, balanced diet, reduction of sugar-sweetened beverages, regular physical activity, management of diabetes, treatment of dyslipidemia, and control of blood pressure. The clinical effect of pomegranate peel is unlikely to be meaningful if it is used without lifestyle correction.

The antifibrotic potential of pomegranate peel is promising but not yet clinically established. Experimental studies demonstrate that pomegranate peel extract can reduce markers of collagen deposition and transforming growth factor beta signaling in animal models [5]. In human liver disease, however, fibrosis develops over years and is influenced by many factors, including viral activity, alcohol exposure, metabolic syndrome, cholestasis, autoimmune inflammation, genetic predisposition, and medication exposure. Therefore, it would be scientifically premature to claim that pomegranate peel reverses human liver fibrosis. At present, it is more accurate to state that pomegranate peel contains compounds with experimental antifibrotic potential that require further clinical verification.

Another important issue is preparation form. Traditional use of dried pomegranate peel as tea or powder differs from standardized hydroalcoholic extract used in clinical trials. The amount of

active compounds in homemade preparations is unpredictable. Overconcentration may increase tannin exposure and gastrointestinal side effects, whereas weak preparations may not provide sufficient bioactive content. Future studies should specify extraction method, dose, active compound standardization, treatment duration, safety monitoring, and target patient group.

Safety considerations are essential in hepatology. Patients with liver disease frequently use multiple medications, including antivirals, statins, antidiabetic drugs, antihypertensive agents, anticoagulants, diuretics, lactulose, rifaximin, and immunosuppressive agents. Any concentrated herbal extract may theoretically interact with drug metabolism or affect tolerability. Moreover, patients with cirrhosis may have altered metabolism, reduced albumin synthesis, coagulopathy, portal hypertension, renal vulnerability, and increased risk of decompensation. For these patients, unsupervised use of concentrated plant extracts is not appropriate.

From a public health perspective, pomegranate peel has additional interest because it is usually considered agricultural waste. Transforming it into a standardized nutraceutical product may have nutritional, economic, and ecological value. However, medical application requires quality control, absence of contaminants, reproducible phytochemical composition, and evidence-based dosage. Without such standards, the same term “pomegranate peel extract” may refer to products with very different biological activity.

Conclusion

Pomegranate peel is a biologically active plant material rich in polyphenols, especially punicalagin and ellagic acid. The available scientific literature suggests that it may have hepatoprotective potential through antioxidant, anti-inflammatory, lipid-modulating, and possible antifibrotic mechanisms. Experimental studies support its protective effects in models of toxic liver injury, fatty liver, and fibrosis. Human clinical trials, although still limited, indicate possible benefits in metabolic fatty liver disease when pomegranate peel extract is used together with dietary intervention.

Despite these promising findings, pomegranate peel should not be presented as an independent treatment for liver diseases. Its most reasonable scientific position is that of an adjunct phytotherapeutic agent that may support standard management in selected patients, particularly those with metabolic fatty liver disease and cardiometabolic risk factors. In viral hepatitis, autoimmune liver disease, cholestatic disorders, alcoholic liver disease, and cirrhosis, etiological and guideline-based treatment remains essential.

Future research should include large randomized controlled trials with standardized extracts, clearly defined doses, longer follow-up periods, liver imaging, fibrosis markers, inflammatory biomarkers, and safety monitoring. Until such evidence becomes stronger, pomegranate peel should be recommended only with caution, preferably under medical supervision, and never as a substitute for proven hepatological treatment.

Practical implications

In clinical and preventive hepatology, pomegranate peel may be discussed as a supportive natural source of polyphenols for patients with metabolic risk factors. Its use is most scientifically justified when combined with weight control, healthy diet, physical activity, and monitoring of liver enzymes and metabolic parameters. Concentrated extracts should be avoided in patients with decompensated cirrhosis, severe cholestasis, unexplained jaundice, pregnancy, lactation, significant polypharmacy, or known intolerance to pomegranate products unless a physician evaluates the risk.

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